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(54) Microporous cellulose membrane

(57) A microporous membrane which has pore diameters of from 0.01 to 5 μm, an ultrafiltration capacity of from 40 to 2000 ml/m² . h . mm Hg and an adjustable exclusion limit for molecular weights of from 70,000 to 3 million and which comprises hydrate cellulose regenerated from cuoxam solutions to which polyethylene glycol having an average molecular weight of from 100 to 1500 has been added is disclosed.

A process for the production of such a membrane which comprises extruding a cellulose cuoxam solution, the spinning solution containing a copper salt in a quantity of from 40 to 60%, by weight, of copper, based on the weight of the cellulose, ammonium in a quantity of from 50 to 300%, by weight, of ammonia, based on the weight of the cellulose, and from 30 to 400%, by weight, based on the weight of the cellulose, of polyethylene glycol having an average molecular weight of from 100 to 1500 and from 4 to 7%, by weight, of cellulose into a coagulation bath is also disclosed.

The present membranes offer certain advantages particularly in plasmaphoresis and microfiltration.

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SPECIFICATION

Microp r us cellulose membrane

This invention relates to a microporous cellulose membrane; more particularly, it relates to a microporous membrane in the form of flat films, tubular films or hollow filaments having pore diameters of from 0.01 to 5 μm and an ultrafiltration capacity of from 40 to 2000 ml/m^2 · h · mm Hg in which the exclusion limit is adjustable for molecular weights of from 70,000 to 3 million.

U.S. Patent No. 1,421,341 describes a filter consisting of a cellulose ester, for example cellulose acetate, and having pores suitable for the separation of bacteria, and also a process for the production of such a filter. The described filters may be dried without the pores collapsing.

The filters are produced by casting a solution of the cellulose ester in a solvent mixture and evaporating the solvent in a moist atmosphere at a low temperature. Water is added to the solvent in such a quantity that the mixture still dissolves the cellulose ester. The quantity of water added affects the size of the pores. The membrane obtained is washed in water, stretched while wet and dried after a heat treatment in hot water or steam.

German Patent No. 843,008 describes a process for the production of ultrafilters and diaphragms of plastics in which porosity is produced by the addition to a plastics solution suitable for producing a thin skin of salts soluble therein or other substances in a solution which is miscible with the plastics solution without entering into a reaction therewith, subsequently drying the mixture and removing the added substance from the skin thus produced by dissolution using a solvent which does not dissolve the plastic.

German Auslegeschrift No. 1,017,596 describes a process in which a cellulose acetate membrane is produced by the phase inversion process comprising pre-gelation in a ventilation chamber at a working temperature of from 20 to 40°C for a relative air humidity of from 50 to 70%.

U.S. Patent No. 2,783,894 describes a similar process for the production of a microporous membrane filter from nylon.

German Auslegeschrift No. 1,156,056 describes a process in which membranes of the type produced in accordance with the above-mentioned U.S. Patent Nos. 1,421,341 or 2,783,894 are applied in a particular way to a hollow body provided with perforations. The microporous films have pores the effective diameter of which is smaller than 10 μm and which, in all, occupy more than 80% of the total volume of the filter material.

German Patent No. 2,257,697 describes a porous cellulose acetate symmetrical membrane filter produced by dissolving cellulose acetate having a degree of acetylation of from 20 to 65.5% in an organic solvent in a ratio, by weight, of from 5 to 40% to the solvent and adding to the solution a diluting solvent, the boiling point of which is higher than that of the above-mentioned organic solvent, and also a metal salt in a ratio, by weight, of from 20 to 200% to the acetate, resulting in the formation of a homogeneous solution which is applied to a flat, polished surface to form a thin film from which the solvent present is removed by evaporation and which is converted by microphase separation into its gel state, after which and finally the metal salt present therein is dissolved out to form the porous membrane.

The pore diameter amounts to from 0.01 to 10 μm and the porosities of from 70 to 81% are mentioned.

When a membrane of the type in question is magnified 6000 times under an electron microscope, it shows a structure which, from its surface, resembles a mat of filaments in which looped filaments projecting from common intersections lie irregularly over and adjacent one another. In cross-section, the structure inside the membrane represents a loose, but uniformly dense mass.

German Offenlegungsschrift No. 2,606,244 describes a hollow fibre for membrane filtration of a synthetic or semi-synthetic, chain-like high polymer which forms filaments when spun, the cylindrical wall forming the hollow fibre, at least in an uninterrupted region resembling a circular band in cross-section, having a three-dimensional net-like structure of fine filter channels having a pore ratio of at least 55% as the active filter zone.

The pores are said to have a diameter of from 1 to 0.01 μm. Particles having a molecular weight of up to 2,400,000 are said to lend themselves to effective separation by the membrane. Membranes of the type in question may b produced fr m cellulose acetate, polyvinyl chloride, polyacrylonitrile or polyamide.

German Offenlegungsschrift No. 2,823,985 describes a dialysis membrane which is distinguished by the fact that it consists of regenerated cellulose regenerated from cuoxam solutions and having an ultrafiltration capacity of from 7 to 30 ml/h · m^2 · mm Hg (corresponding to from 14 to 60 pm · s^{-1} · Pa^{-1}) and an average molecule permeability of from 4 · 10^3 to 12 · 10^{-3} cm/min (corresponding to from 0.65 to 2.0 μm · s^{-1}).

According to German Offenlegungsschrift No. 28,23 985, membranes of the type in question

may be produced by a process in which finely ground CuO is added to a cellulose-cuoxam solution and washed out again with hot sulphuric acid after coagulation. In a membrane of this type, the molecular weight exclusion limit is below 60,000 because the passage of blood proteins and other high molecular weight c nstituents of blood is effectively prevented and the molecular weight of the albumin in blood amounts to from 60,000 to 70,000.

Although there are may types of microporous membranes the pores of which may be adjusted in the required manner by various measures, there was a considerable need to produce a membrane of this type from hydrate cellulose regenerated from cuoxam solutions. The results of tests which have been conducted so far have mostly been negative or are comparable with the results obtained, for example, with the membranes according to German Offenlegungsschrift No. 2,823,985. In these tests, alcohols, such as methanol, ethanol and isopropanol, and also glycols, such as propylene glycol and butyl glycol, also such compounds as dimethyl formamide, ethoxylated fatty alcohols and nonyl phenyl polyglycol ethers, were added to the cellulose-cuoxam solution, but did not improve effectiveness by comparison with microfilters or increase the exclusion limit. With polypropylene glycols (molecular weight 1200; ratio of PPG to cellulose 0.1 to 1) it was not possible to produce a homogeneous spinning solution.

By virtue of the particularly high compatibility with blood of regenerated cellulose regenerated from cuoxam solutions, there have been repeated demands in specialist circles for a microporous membrane comparable in its filter properties to known microporous membranes to be produced from regenerated cellulose. Accordingly, there has also been no shortage of attempts to produce such a membrane. Although may other spinning solution additives have been tested, none has proved successful. In addition to the substances mentioned, long-chain fatty alcohols, esters, dioxane, quaternary ammonium salts, casein, silica gel and zeolites have also been added to the spinning solution in various concentrations, but without any success.

In some cases, it was not possible to prepare homogeneous mixtures of the above-mentioned substances with the cuoxam solution. Although some of the mixtures were homogeneous, they could not be spun. However, some of the additives even resulted in coagulation of the cuoxam solution. A homogeneous spinning solution is to be understood to be a solution in which no phase separation is discernible to the naked eye.

It has now surprisingly been found that it is possible after all to produce a microporous membrane in the form of flat films, tubular films or hollow filaments having pore diameters of from 0.01 to 5 μm and an ultrafiltration capacity of from 40 to 2000 $ml/m^2 \cdot h \cdot mm\ Hg$, in which the exclusion limit is adjustable for molecular weights of from 70,000 to 3 million and which is characterised in that it consists of hydrate cellulose regenerated from cuoxam solutions to which polyether glycol having an average molecular weight of from 100 to 1500 has been added. Since the addition of a relatively large number of substances to cuoxam solutions did not result in the formation of microporous membranes comparable with the known microporous membranes, it was also surprising to find that it is possible to produce such membranes by the process according to the present invention which is distringuished by the fact that the spinning solution contains a copper salt in a quantity of from 40 to 60%, by weight, of copper, based on the weight of the cellulose, ammonium in a quantity of from 50 to 300%, by weight, of ammonia, based on the weight of the cellulose, from 30 to 400%, by weight, based on the weight of the cellulose, of polyethylene glycol having an average molecular weight of from 100 to 1500 and from 4 to 7%, by weight, of cellulose.

In one embodiment, the cellulose is coagulated in an acid medium. In this embodiment, therefore, the process according to the present invention is further distinguished by the fact that a water-diluted acid is used as the coagulation bath.

Dilute sulphuric acid is preferably used for the coagulation bath. In this embodiment of the present invention, the concentration of sulphuric acid amounts to from 30 to 300 g/l. Coagulation is preferably carried out at slightly higher temperatures, the temperature of the coagulation bath being from 30 to 65°C.

Where coagulation of the cellulose-cuoxam solution is carried out in an acid medium, it has been found that the ultrafiltration capacity increases to an unexpected extent for standard wall thicknesses of the microporous membrane. Accordingly, it is possible to produce microporous membranes which have very high ultrafiltration capacities and, at the same time, relatively thick membrane walls. The greater wall thickness of the membrane naturally provides it with correspondingly greater strength.

In some of the applications for microporous membranes, it is desirable to use membranes having a relatively low molecular weight exclusion limit and, correspondingly, a relatively low molecular weight capacity. Membranes of this type may be advantageously produced in another embodiment in which coagulation is carried out in an alkaline medium. In this embodiment, therefore, the process according to th present invention is further distinguished by the fact that a water-dilute alkali metal hydroxide is used as the coagulation bath.

The coagulation bath is preferably formed by dilute sodium hydroxide. In this mbodiment of the present invention, the concentration of the sodium hydroxide is from 60 to 140 g/l.

Where alkaline coagulation baths are used, th process according to the present invention is carried out in such a way that the temp rature f th coagulati n bath is from 15 to 30°C.

The temperature is preferably from 20 to 25°C.

The polyethylene glycol used may b optimally mixed in if the rati , by weight, of polyethylene glycol to cellulose is lower than calculated in accordance with the following equation:

$$V = -\frac{0.59}{\log MW} - 3.3 \cdot \log MW + 10.9$$

wherein MW is the molecular weight of the polyethylene glycol used.

It is of particular advantage to prepare the spinning solution by mixing and homogenising a cellulose-cuoxam solution having a correspondingly higher cellulose concentration with a solution of polyethylene glycol in water and ammonia.

The cellulose-cuoxam solution is preferably mixed and homogenised with the solution of polyethylene glycol in ammonia immediately before the spinneret.

The purpose for which the microporous membrane according to the present invention may be used with particular advantage by virtue of the high compatibility with blood of cellulose regenerated by the cuoxam process is plasmaphoresis, i.e. the separation of blood plasma from cellular constituents, and also the further separation of plasma constituents according to molecular weight.

By virtue of the hydrophilic character of cellulose and hence of the membrane according to the present invention, the present membrane may be used particularly successfully for microfiltration, for example for the sterilisation of aqueous solutions or suspensions and for the treatment of effluents.

Where it is used for haemodialysis and haemofiltration the membrane should not allow any proteins to pass through. Albumin is the most common protein in plasma and has the lowest molecular weight (approximately 68,000). Accordingly, the membrane must be impermeable to molecules of this size in haemodialysis and haemofiltration.

Medicinal research has shown that some illnesses are caused by toxins which are frequently fixed to proteins, but which themselves are small molecules which would easily pass through the above-mentioned dialysis and haemofiltration membranes if they were present in free form. However, the fact that they are fixed to proteins means that they represent such large molecules that they cannot be eliminated by standard dialysis membranes. Immuno-complexes and antigens also have correspondingly high molecular weights.

Hitherto, protein-fixed toxins of this type having molecular weights of from 100,000 to 3 million have largely been removed by the method of plasma separation using ultracentrifuges.

However, there are also a few types of membrane which have been used for this purpose, including in particular cellulose acetate, cellulose nitrate and polyvinyl alcohol membranes. However, membranes of this type have more of a decelerated or, more precisely, only partial permeability to the above-mentioned proteins. Permeability may be expressed by the so-called screening coefficient:

$$S = \frac{C_F}{C_B}$$

wherein

C_F is the concentration of the substance X in the filtrate and

C_B is the concentration of the substance X in the blood.

The screening coefficient may be determined for example by laser-nephelometric methods. If S = 1, complete permeability prevails. If S is less than 1, partial permeability prevails. The membranes available at the present time have screening coefficients which, even for albumin, amount to less than 0.8. This means that the constituents to be separated are only eliminated to a reduced extent. Because of this, a longer treatment time is required. It is also necessary to use larger quantities of reinfusions or very larg membranes which involves considerable disadvantages because, in that case, the modules have a very high extracorporeal volume.

In addition to the screening c ffici nt, the ultrafiltration capacity is a measure of the p rmeability properti s of a membrane. The ultrafiltration capacity of a membrane is determined by measuring the volume of liquid which flows through the membrane over an area determined by the apparatus for a given pressure difference and at a temperature of 37°C and which, for the purpose of general comparability, is standardised to unit area, unit time and unit pressure.

Physiological saline is used as the liquid. The method in question is described in "Evaluation of Hemodialyzers and Dialysis Membranes" issued by the U.S. Department of H alth, Education and Welfare, DHEW Publication N . (NIH) 77–1294, pages 24 to 26.

If a protein solution, for xample a 1% albumin solution, is used instead of the physiological saline, trans-membrane flow of the corresponding protein through the membrane is obtained for a given pressure difference, for example 0.1 bar.

The present invention is illustrated by the following Examples which show in particular how any change in the process conditions affects the microporous membrane.

EXAMPLE 1

A cellulose-cuoxam solution containing 9.2%, by weight, of cellulose, 6.2%, by weight, of NH_3 and 3.9%, by weight, of Cu (in the form of $Cu(NH_4)_3SO_4$) and water was prepared and dearated. The solution had a density of 1.08 g/cc. A solution was prepared from 10 litres of a 30% ammonia solution, 5 litres of polethylene glycol (MW 400) and 2 litres of water and delivered by means of a metering pump to a "Pentax" mixer at a rate of 164 ml/minute. At the same time, 180 ml/minute of the cellulose cuoxam solution was delivered to the "Pentax" mixer and mixed and homogenised therein to form a spinning solution containing 5.1%, by weight, of cellulose, 11.0%, by weight, of NH_3, 15.0%, by weight, of PEG and 2,16%, by weight, of Cu. The spinning solution was then extruded through the annular slot of a hollow-filament spinneret into a coagulation bath containing 112 g/l of NaOH at 25°C while at the same time isopropyl myristate was delivered to the central bore of the spinneret. The spinning rate amounted to 42 m/minute. The hollow-filament membrane obtained has the following properties after the removal of copper, washing, softening in a softening bath containing 25 g/l of glycerol and 400 g/l of isopropanol in water and drying in air at 90°C:

External diameter	260 μm
Internal diameter	220 μm
Tensile strength	$18.1 \cdot 10^3$ cN/mm^2
Breaking elongation	27.5%
Ultrafiltration capacity	271 ml/m^2 · h · mm Hg

The same spinning solution was extruded into a coagulation bath containing 80 g/l of H_2SO_4 at 30°C under otherwise the same conditions.

The hollow-filament membrane formed had the following properties:

External diameter	329 μm
Internal diameter	227 μm
Tensile strength	$13.3 \cdot 10^3$ cN/mm^2
Breaking elongation	31.7 %
Ultrafiltration capacity	901 ml/m^2 · h · mm Hg
Screening coefficient for albumin MW 68,000	100%
Transmembrane flow 1% of albumin, 0.1 bar =	580 ml/min · m^2

EXAMPLE 2

Following the same procedure as in Example 1, 180 ml/minute of the deaerated cellulose-cuoxam solution and 164 ml/minute of a solution of 10 litres of 30 % ammonia solution, 1.7 litre of polyethylene glycol (MW 400) and 5.3 litres of water were delivered to the "Pentax"-mixer and the resulting mixture spun at a rate of 42 m/minute to form hollow-filament membranes. The spinning solution had the following composition: 5.12%, by weight, of cellulose, 5,12%, by weight, of polyethylene glycol, 2.17% by weight, of Cu and 11.16%, by weight, of NH_3. If a dilute sodium hydroxide solution having a concentration of 112 g/l NaOH and a temperature of 25°C is used as the coagulation bath, a hollow-filament membrane having the following properties is obtained after the removal of copper, washing, softening and drying:

External diameter	244 μm
Internal diameter	210 μm
Tensile strength	$17.8 \cdot 10^3$ cN/mm^2
Br aking longation	31.1%
Ultrafiltration capacity	32.8 ml/m^2 · h · mm Hg

If the spinning solution is spun into an acid coagulation bath containing 180 g/1 of H_2SO_4 at

45°C under otherwise the same conditions, the hollow-filam nt membrane has the following properties after the removal of copper, washing, softening and drying:

External diameter	320 μm
Internal diameter	210 μm
Tensile strength	$14.0 \cdot 10^3$ cN/mm²
Breaking elongation	27.0%
Ultrafiltration capacity	301 ml/m² · h · mm Hg
Screening coefficient for albumin MW 68,000	99.2%
Transmembrane flow for 1% albumin, 0.1 bar =	253 ml/min · m²

EXAMPLE 3

Comparison of the ultrafiltration capacities obtained with different concentrations of ammonia in the spinning solution and with different wall thicknesses reveals characteristic differences depending on the precipitation medium used and on whether the spinning solution was spun into an alkaline coagulation bath or into an acid coagulation bath. The cellulose content of the spinning solutions amounted to 5.1%, by weight, the copper content of 42.4%, based on the celloluse content, and the polyethylene (molecular weight 400) content to 295%, based on the cellulose content. The NH_3–content amounted to from 70 to 255%. based on the cellulose content. The ultrafiltration capacity was measured in dependence upon the wall thickness of the hollow filaments. Production was carried out under otherwise the same conditions as in Examples 1 and 2. The results are set out in the following Table.

	NH_3	Wall thickness (μm)	Coagulation	Ultrafiltration capacity ml/m² · h · mm Hg
a	70.6%	4	65 g/l of NaOH	35
b	70.6%	16	65 g/l of NaOH	15
c	70.6%	9	180 g/l of H_2SO_4	350
d	70.6%	16	180 g/l of H_2SO_4	160
e	120 %	16	65 g/l of NaOH	75
f	120 %	4	65 g/l of NaOH	25
g	120 %	9	180 g/l of H_2SO_4	400
h	120 %	40	180 g/l of H_2SO_4	30
i	198 %	16	65 g/l of NaOH	110
k	198 %	4	65 g/l of NaOH	50
l	198 %	7	180 g/l of H_2SO_4	720
m	198 %	32	180 g/l of H_2SO_4	125
n	225 %	18	65 g/l of NaOH	130
o	225 %	4	65 g/l of NaOH	60
p	225 %	13	180 g/l of H_2SO_4	1000
q	225 %	18	180 g/l of H_2SO_4	160

CLAIMS

1. A microporous membrane which has pore diameters of from 0.01 to 5 μm, an ultrafiltration capacity of from 40 to 2000 ml/m² · h · mm Hg and an adjustable exclusion limit for molecular weights of from 70,000 to 3 million and which comprises hydrate cellulose regenerated from cuoxam solutions to which polyethylene glycol having an average molecular weight of from 100 to 1500 has been added.

2. A membrane as claimed in claim 1 in the form of flat films, tubular films or hollow filaments.

3. A membrane as claimed in claim 1 substantially as her in described.

4. A process for the production of a m mbrane as claimed in claim 1 which comprises extruding a cellulose-cuoxam solution, the spinning solution containing a copper salt in a quantity of from 40 to 60%, by weight, of copper, based on the weight of the cellulose, ammonium in a quantity of from 50 to 300%, by weight, of ammonia, based on the weight of the cellulose, and from 30 to 400%, by weight, based on the w ight of the cellulose, of polyethylene glycol having an averag molecular weight f from 100 to 1500 and fr m 4 to 7%, by weight, of cellulose into a coagulation bath.

5. A process as claimed in claim 4, in which an acid diluted with water is used as th coagulation bath.

6. A process as claimed in claim 5, in which the coagulation bath comprises dilute sulphuric acid.

7. A process as claimed in claim 6, in which the concentration of sulphuric acid amounts to from 30 to 300 g/l.

8. A process as claimed in any of claims 4 to 7 in which the temperature of the coagulation bath is from 30 to 65°C.

9. A process as claimed in claim 4, in which a water-diluted alkali metal hydroxide is used as the coagulation bath.

10. A process as claimed in claim 9 in which the coagulation bath comprises dilute sodium hydroxide.

11. A process as claimed in claim 10, in which the concentration of the sodium hydroxide amounts to from 20 to 200 g/l.

12. A process as claimed in claim 11, in which the concentration of the sodium hydroxide amounts to from 60 to 140 g/l.

13. A process as claimed in any of claims 4 or 9 to 12 in which the temeprature of the coagulation bath is from 15 to 30°C.

14. A process as claimed in claim 13, in which the temperature is from 20 to 25°C.

15. A process as claimed in any of claims 4 to 14, in which the ratio, by weight, of polyethylene glycol to cellulose is lower than calculated in accordance with the following equation:

$$V = -\frac{0.59}{\log MW} - 3.3 \cdot \log MW + 10.9$$

wherein MW is the molecular weight of the polyethylene glycol used.

16. A process as claimed in any of claims 4 to 15, in which the spinning solution is prepared by mixing and homogenising a cellulose-cuoxam solution having a correspondingly higher cellulose concentration with a solution of polyethylene glycol in water and ammonia.

17. A process as claimed in claim 16, in which the cellulose-cuoxam solution is mixed and homogenised with the solution of polyethylene glycol in ammonia immediately before extrusion through a spinneret.

18. A process as claimed in claim 4 substantially as herein described.

19. The use of a membrane as claimed in any of claims 1 to 3 for plasmaphoresis.

20. The use of a membrane as claimed in any of claims 1 to 3 for microfiltration.

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